Holographic Microscopy with Acoustic Modulation for Detection of Nano-sized Particles and Pathogens in Solution

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Abstract: We present a method for the detection of nanoparticles in solution using an acoustically actuated holographic microscope. This type of microscopy can be used for high-throughput biosensing applications, e.g., detection of viruses in a liquid.
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1. Introduction

Detection and characterization of label-free nanoparticles is of immense importance in many areas of bio-medical sciences, but still remains a significant challenge till this day. It requires complex and expensive imaging systems such as atomic force microscopy, scanning and transmission electron microscopy or optical methods such as super-resolution microscopy, dark field microscopy, nanoparticle tracking analysis etc. Most importantly, a majority of these techniques can only be applied to dry samples, thus limiting their applications, especially in bio-medical and polymer sciences.

Here we present a high-throughput method of detecting nanoparticles in solution using an acoustically actuated holographic microscope. This is an interferometric method based on in-line holography[1]. The in-line holograms, formed due to the interference between the transmitted and the scattered light from each nanoparticle, are digitally recorded to retrieve different information about the sample. One of the significant challenges in detecting nano-sized particles is their weak light scattering. Here we mitigate this by creating liquid lens like structures assembled around the nanoparticles using surface acoustic waves. This method enabled us to detect particles below 200 nm in size including viruses and bacteria. In addition to detecting nanoparticles, this system is capable of distinguishing specific vs. non-specific binding which is a significant challenge for any bio-sensor. This type of a field-portable detection system will provide a low-cost and high-throughput readout for different biosensing applications.

2. Methods

Our detection system consists of a lens-free holographic microscope and an interdigitated transducer (IDT) as shown in Figure 1. The IDT was coupled to a disposable chip containing the nanoparticles in a thin film of liquid. A signal generator was used to drive the IDT which generates surface acoustic waves coupled to the sample solution. The nanoparticles were detected using a holographic microscope which was 3D printed (Fig. 1) and consists of an illumination unit and a complementary metal-oxide-semiconductor (CMOS) imager chip with a pixel size of 1.67μm [2,3]. The illumination unit consists of 20 different fiber-coupled light emitting diodes (LEDs), individually controlled by a micro-controller. The light from the LED was passed through an optical band-pass filter and illuminated the sample. The in-line holograms were then recorded using the CMOS chip placed close (<1mm) to the sample. The sample under test was continuously illuminated and the holographic images were recorded before and after turning on the IDT. The validation experiments were performed using a scanning electron microscope.

3. Results

Nanoparticles have weak optical scattering cross-section and thus are difficult to detect. It becomes even more challenging in solution due to partial refractive index matching. Thus we do not observe these nanoparticles using our holographic microscope before turning on the SAW. The SAW, generated by the IDT, is coupled into the thin film of liquid on the disposable chip, which results in the creation of standing waves due to the finite geometry of the chip. The waves displaces the liquid from the surface around the pressure nodes thereby creating localized lens like liquid droplets around the nanoparticles as shown in Figure 1 (inset). Our numerical simulations show that these nanolenses extend several hundred nm beyond the particle. For example, for a 200nm particle these structures

can extend up to 600nm, making the size of the nanoparticle-nanolens complex > 1μm. These structures enhance the optical scattering from the nanoparticles, thereby increasing the signal to noise ratio (SNR) to make them distinguishable from the background. After the SAW is turned off the liquid relaxes back to the original position making the particles invisible again. Some of the holograms of 200nm particles when the SAW is turned on are shown in Figure 2 along with their SEM images (used for validation).

Another interesting aspect of this technique is the ability of the SAW to move/clean up non-specifically bound particles on the substrate. By using antibody-coated chips we can specifically bind the pathogen of interest and use SAW to move any non-specifically attached particle on the surface of the sensor. Thus by performing differential imaging (i.e., before and after SAW) we can detect the non-specifically bound particles and digitally eliminate them, without using any surface blockers or special surface treatment.

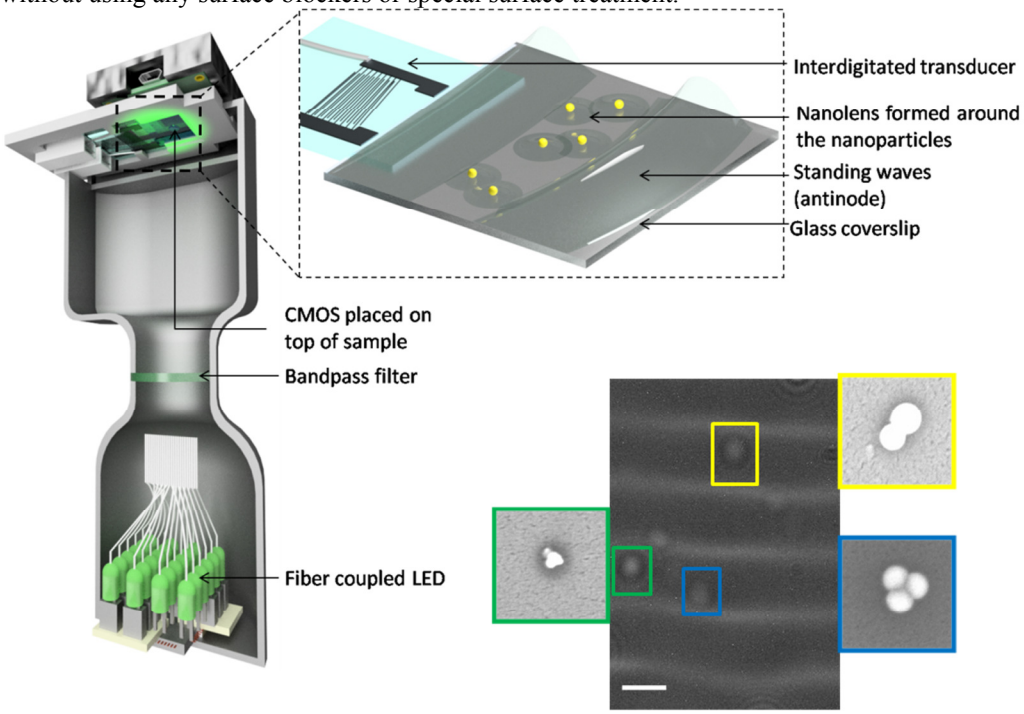

Figure. 1. Schematics of the acoustically actuated holographic microscope. Inset: Schematic showing the formation of the nanolenses when the SAW is coupled to the sample.

Figure 2. Image of the coverslip with 200nm polystyrene nanoparticles during acoustic actuation. Insets: SEM images of the corresponding nanoparticles, used for cross-validation (field-of-view of SEM images: 1μm × 1μm).

4. Conclusions

We presented a high-throughput method to detect nanoparticles in solution using a low-cost and portable lens-free microscope coupled to an IDT. We used surface acoustic waves for actuation and creation of lens like structures around the nanoparticles that enable their detection. Our approach can also be used to digitally mitigate non-specific binding, a fundamental problem in biosensing. This system can be readily integrated into lab-on-chip devices for a variety of biosensing applications related to infectious diseases, among others.

5. References

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